Is Cangrelor hype or hope in STEMI primary PCI?

ARUN KALYANASUNDARAM MD, MPH, FSCAI
HOPE
Issues with platelet inhibition in STEMI
Delayed onset

In acute settings, achieving the expected antiplatelet effect with oral administration may not be feasible due to:

• delayed bioavailability\textsuperscript{1-3}
• morphine use\textsuperscript{4,5}
• mechanical ventilation\textsuperscript{5}
• active vomiting\textsuperscript{6}
• cardiogenic shock\textsuperscript{7}
• heavy sedation\textsuperscript{8}
• therapeutic hypothermia\textsuperscript{8}

Issues with platelet inhibition in STEMI
Delayed offset

Approximately 11% of ACS patients may require surgical revascularization¹

Oral P2Y₁₂ inhibitors may require 3 to 9 days for return of platelet function.²-⁴

Universal pretreatment before angiography in these patients could lead to the following:

• increased risk of bleeding in case of CABG⁴
• increased need for transfusion⁵
• increased hospital stay⁶

Cangrelor

- Direct platelet P2Y$_{12}$ receptor antagonist
- ATP analogue MW=800 Daltons
- Parenteral administration
- T1/2 = 3 to 6 minutes
- Offset = 60 minutes
Cangrelor
Unique PK/PD Profile

Akers W et al., *J. Clin. Pharmacol.* 2010; 50; 27
Cangrelor

Proposed Practical Benefits of an IV P2Y$_{12}$ Inhibitor

- **Fast Onset**
  - No need for preloading
  - Informed treatment after angiography
  - Limit unnecessary exposures

- **Fast Offset**
  - No delay to CABG

- **IV Administration**
  - Ideal for patients unable to take PO

![Graph showing Platelet Reactivity (PRU) over time with Cangrelor infusion and PCI procedures.](image-url)
CHAMPION Trials Study Designs

Randomized, Double Blind, Controlled Trials of patients undergoing PCI

**CHAMPION PHOENIX**
- n=10,942 mITT
- SA / NSTE-ACS / STEMI
- P2Y12 naïve
- Placebo or clopidogrel before or after PCI

**CHAMPION PCI**
- n=8667 mITT
- SA / NSTE-ACS / STEMI
- Placebo or clopidogrel before PCI

**CHAMPION PLATFORM**
- n=5301 mITT
- SA / NSTE-ACS
- P2Y12 naïve
- Placebo or clopidogrel after PCI

Cangrelor bolus then infusion
- OR
- Clopidogrel 600 mg or 300 mg oral

Clopidogrel 600 mg oral

Death, MI, ischemia-driven revascularization

SCAI

SACIS 2016
Death/ MI/ IDR/ Stent Thrombosis within 48 Hours (all CHAMPION TRIALS)

No. patients at risk
Cangrelor: 12,475 12,053 12,040 12,033 12,021 12,006 12,002 11,994 11,985
Clopidogrel: 12,435 11,903 11,897 11,891 11,882 11,874 11,866 11,853 11,843

Log-rank p value=0.0007

Cangrelor: 3.8%
Clopidogrel: 4.7%

Stent Thrombosis within 48 Hours
(CHAMPION TRIALS)

<table>
<thead>
<tr>
<th>Hours from randomization</th>
<th>Cangrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. patients at risk</td>
<td>Event rate (%)</td>
</tr>
<tr>
<td></td>
<td>Cangrelor: 12,475 12,420 12,406 12,403 12,395 12,387 12,384 12,377 12,371</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel: 12,435 12,327 12,319 12,318 12,308 12,306 12,304 12,297 12,291</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

### CHAMPION - PHOENIX
Overall and STEMI outcomes, 48 h

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Cangrelor</th>
<th>Clopidogrel</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mITT (N=10,942)</td>
<td>257/5470 (4.7%)</td>
<td>322/5469 (5.9%)</td>
<td>0.78 (0.66–0.93)</td>
</tr>
<tr>
<td>STEMI (n=1,991)</td>
<td>27/961 (2.8%)</td>
<td>38/1030 (3.7%)</td>
<td>0.75 (0.46–1.25)</td>
</tr>
</tbody>
</table>

**Stent thrombosis**

| Overall mITT (N=10,942)   | 46/5470 (0.8%) | 74/5469 (1.4%) | 0.62 (0.43–0.90) |
| STEMI (n=1,991)           | 12/961 (1.2%)  | 20/1030 (1.9%) | 0.64 (0.31–1.31) |

**GUSTO sev/mod bleeding**

| Overall safety (N=11,056) | 31/5529 (0.6%) | 19/5527 (0.3%) | 1.63 (0.92–2.90) |
| STEMI (n=2,070)           | 12/1000 (1.2%) | 7/1070 (0.7%)  | 1.84 (0.72, 4.70) |

Bhatt DL et al NEJM 2013;68:1303-13; and suppl appendix
Pooled CHAMPION Trials
Overall and STEMI outcomes, 48 h

Primary Endpoint

<table>
<thead>
<tr>
<th>Overall mITT* (N=24,910)</th>
<th>Cangrelor</th>
<th>Clopidogrel</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>473/12,459 (3.8%)</td>
<td>579/12,422 (4.7%)</td>
<td>0.81 (0.71–0.91)</td>
</tr>
<tr>
<td>STEMI† (n=2884)</td>
<td>41/1407 (2.9%)</td>
<td>51/1477 (3.5%)</td>
<td>0.84 (0.55–1.27)</td>
</tr>
</tbody>
</table>

Stent thrombosis

<table>
<thead>
<tr>
<th>Overall mITT* (N=24,881)</th>
<th>Cangrelor</th>
<th>Clopidogrel</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>62/12,459 (0.5%)</td>
<td>105/12,422 (0.8%)</td>
<td>0.59 (0.43–0.80)</td>
</tr>
<tr>
<td>STEMI (n=2,884)</td>
<td>16/1407 (1.1%)</td>
<td>24/1477 (1.6%)</td>
<td>0.70 (0.37—1.32)</td>
</tr>
</tbody>
</table>

GUSTO sev/mod bleeding

<table>
<thead>
<tr>
<th>Overall safety* (N=25,107)</th>
<th>Cangrelor</th>
<th>Clopidogrel</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>103 (0.8%)</td>
<td>79 (0.6%)</td>
<td>1.30 (0.97–1.75)</td>
</tr>
<tr>
<td>STEMI (n=3008)</td>
<td>17/1463 (1.2%)</td>
<td>15/1545 (1.0%)</td>
<td>1.20 (0.60 - 2.41)</td>
</tr>
</tbody>
</table>

* Overall population includes CHAMPION PHOENIX, PCI and PLATFORM ; †STEMI population from PHOENIX and PCI
PHOENIX: Death/MI-SCAI/Ischemia driven revascularization /Stent thrombosis-ARC

Time to events from PCI start

Endpoints
- Death
- SCAI MI
- Ischaemia driven revascularisation
- ARC-Stent thrombosis

Treatment 1= cangrelor  2= clopidogrel

Treatment

Time (Hrs)
Oral P2Y12 effects in STEMI patients

55 patients undergoing primary PCI, randomized to prasugrel or ticagrelor.


SCAI SACIS 2016

Individual values of platelet reactivity at 0, 1, 2, 6, 24 hours, and Day 5 postrandomization, as assessed with the VerifyNow assay in P2Y12 reaction units (PRU) (A) and with Multiplate analyzer in aggregation units (AU)/min (B).
Morphine Is Associated With a Delayed Activity of Oral Antiplatelet Agents in Patients With ST-Elevation Acute Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

No difference between prasugrel and ticagrelor patients (39% vs 37%; p = 0.719).

SCAI SACIS 2016
PLATO
Stent Thrombosis in 11,284 ACS Patients

Timing of Definite ST

<table>
<thead>
<tr>
<th>Timing of Definite ST</th>
<th>HR [95% CI] Favoring Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (≤24 hours)</td>
<td>0.94 [0.43 – 2.05]</td>
</tr>
<tr>
<td>Subacute (1-30 days)</td>
<td>0.60 [0.39 – 0.93]</td>
</tr>
<tr>
<td>Late (30 days-1 year)</td>
<td>0.48 [0.24 – 0.96]</td>
</tr>
</tbody>
</table>

No reduction in acute stent thrombosis

Early Stent Thrombosis

- Clopidogrel
- Prasugrel

HR 0.41 [0.29-0.59]
P < 0.0001
1.6%

Late Stent Thrombosis

- Clopidogrel
- Prasugrel

HR 0.60 [0.37-0.97]
P = 0.03
0.8%

No reduction in acute (≤24 hrs) stent thrombosis

Intra-procedural Stent Thrombosis (IPST)

Defined as new or increasing thrombus within or adjacent to a deployed stent occurring during the index PCI procedure, as assessed by an angiographic core lab using frame-by-frame analysis.

6,591 pts assessed in ACUITY (NSTE-ACS) and HORIZONS-AMI (STEMI)

Frequency of IPST

<table>
<thead>
<tr>
<th>Year</th>
<th>Frequency</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.7%</td>
<td>47/6591</td>
</tr>
<tr>
<td>2</td>
<td>1.2%</td>
<td>37/3173</td>
</tr>
<tr>
<td>3</td>
<td>0.3%</td>
<td>10/3428</td>
</tr>
</tbody>
</table>

P<0.001
IPST in CHAMPION PHOENIX

10,939 pts assessed by a blinded core lab
Impact on 30-day mortality

![Graph showing the impact of IPST on 30-day mortality.]

**IPST:**
- 89, 84, 82, 80, 80, 80, 79

**No IPST:**
- 10850, 10781, 10759, 10741, 10735, 10727, 10688

**Mortality (%)**
- 0, 2, 4, 6, 8, 10, 12

**Days from Randomization**
- 0, 5, 10, 15, 20, 25, 30

**Impact on 30-day mortality**
- HR [95%CI] = 11.04 [5.59, 21.79]
- P < 0.0001

# IPST in CHAMPION PHOENIX

10,939 pts assessed by a blinded core lab

Impact of IPST on adverse events: *Pts with TIMI 3 flow*

<table>
<thead>
<tr>
<th>48-hour endpoints</th>
<th>IPST</th>
<th>No IPST</th>
<th>Adjusted OR [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/MI/IDR/ARC-ST</td>
<td>26.1%</td>
<td>4.3%</td>
<td>10.24 [5.64,18.60]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death</td>
<td>2.9%</td>
<td>0.2%</td>
<td>15.95 [3.38,75.35]</td>
<td>0.0005</td>
</tr>
<tr>
<td>ARC Definite ST</td>
<td>4.3%</td>
<td>0.2%</td>
<td>20.58 [5.64,75.08]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IDR</td>
<td>5.8%</td>
<td>0.4%</td>
<td>15.50 [5.15,46.62]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MI</td>
<td>23.2%</td>
<td>4.0%</td>
<td>9.74 [5.21,18.19]</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>30-day endpoints</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/MI/IDR/ARC-ST</td>
<td>29.0%</td>
<td>5.4%</td>
<td>8.85 [5.00,15.65]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death</td>
<td>5.8%</td>
<td>0.8%</td>
<td>8.55 [2.94,24.84]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ARC ST</td>
<td>7.2%</td>
<td>0.7%</td>
<td>12.28 [4.64,32.55]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ARC Definite ST</td>
<td>5.8%</td>
<td>0.5%</td>
<td>12.94 [4.36,38.39]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IDR</td>
<td>7.2%</td>
<td>0.9%</td>
<td>8.87 [3.39,23.17]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MI</td>
<td>24.6%</td>
<td>4.2%</td>
<td>9.66 [5.25,17.76]</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Propensity score adjusted for: age, gender, smoker, region US vs. OUS, race, weight, biomarker, previous MI, (stable angina vs. NSTEMI vs. STEMI), previous PCI, previous CABG, peripheral artery disease, patient presentation, worst pre-procedure TIMI score, stent type, bifurcation treatment, aspirin dose, number of treated vessels, clopidogrel loading received, clopidogrel loading dose (300 vs. 600 mg), cangrelor infusion duration, bivalirudin received.

IPST in CHAMPION PHOENIX

10,939 pts assessed by a blinded core lab

Length of Stay from PCI

**IPST in CHAMPION PHOENIX**

10,939 pts assessed by a blinded core lab

**Reduction of IPST with cangrelor**

**IPST (%)**

- **Clopidogrel (n=5470)**
- **Cangrelor (n=5469)**

**OR 0.65 [0.42,0.99] p=0.04**

**OR 0.50 [0.24,1.05] p=0.06**

**OR 0.75 [0.38,1.50] p=0.42**

**OR 0.76 [0.34,1.73] p=0.52**

\[P_{Int} = 0.77\]

- **All**
  - 1.0
  - 0.6

- **Stable Angina**
  - 0.7
  - 0.4

- **NSTE-ACS**
  - 1.3
  - 1.0

- **STEMI**
  - 1.4
  - 1.0

Conclusions: Intra-procedural Stent Thrombosis

- IPST is a major adverse clinical event that has serious implications for patient prognosis

- No oral ADP antagonist has been demonstrated to reduce IPST
REASON FOR HOPE

• Pharmacokinetics: yes
• Pharmacodynamics: yes
• Clinical need: yes
• Clinical outcomes
  • Ischemic events: yes
  • Bleeding: yes
HYPE
# Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio (95% CI)</th>
<th>Total Patients</th>
<th>KM % at Month 12</th>
<th>HR (95% CI)</th>
<th>P value (Interaction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Treatment Effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New ST elevation/LBBB at rand.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>11074</td>
<td>10.1</td>
<td>0.83 (0.74, 0.93)</td>
<td>0.68</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>7544</td>
<td>9.4</td>
<td>0.87 (0.75, 1.01)</td>
<td></td>
</tr>
<tr>
<td>Final Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td></td>
<td>3112</td>
<td>8.6</td>
<td>0.96 (0.75, 1.22)</td>
<td></td>
</tr>
<tr>
<td>NSTEMI</td>
<td></td>
<td>7955</td>
<td>11.4</td>
<td>0.83 (0.73, 0.94)</td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td></td>
<td>7026</td>
<td>8.5</td>
<td>0.84 (0.72, 0.98)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>489</td>
<td>9.1</td>
<td>0.58 (0.34, 1.00)</td>
<td></td>
</tr>
</tbody>
</table>
At 30 days, 115 (6.5%) individuals assigned prasugrel had met the primary endpoint compared with 166 (9.5%) allocated clopidogrel (hazard ratio 0.68 [95% CI 0.54–0.87]; p=0.0017).
Early P2Y_{12} inhibition in ST-segment elevation myocardial infarction: Bridging the gap
Double Versus Standard Loading Dose of Ticagrelor
Onset of Antiplatelet Action in Patients With STEMI
Undergoing Primary PCI

Comparison of double (360 mg) ticagrelor loading dose with standard (60 mg) prasugrel loading dose in ST-elevation myocardial infarction patients: The Rapid Activity of Platelet Inhibitor Drugs (RAPID) primary PCI 2 study


SCAI
SACIS 2016
The graph shows the P2Y12 reactivity units over time for crushed and integral forms. The y-axis represents P2Y12 reactivity units, and the x-axis represents time points at baseline, 1 h, 2 h, 4 h, and 8 h.

- The green line represents the crushed form, and the orange line represents the integral form.

At 1 h, there is a significant decrease in reactivity units, indicated by an asterisk (*). The asterisk indicates a statistically significant difference at p=0.006.

The graph is from the MOJITO Study, and the reference is Parodi G et al. J Am Coll Cardiol 2015.

Additional context: This graph is from SCAI SACIS 2016.
"Data are lacking on the combination of the early use of ticagrelor (at the first medical contact) and administration of the crushed form of the drug"
WHAT DO WE KNOW?

Oral P2Y12 inhibitors represents the current “standard of care,” although suboptimal platelet inhibition during and shortly after the procedure has been documented.
1. What Kind of Trials would we need to prove this Hypothesis?

Randomized Trials with STEMI and Primary PCI:
- Cangrelor vs. Ticagrelor
- Cangrelor vs. Prasugrel

*do not exist!*
Pivotal Studies with these three P2Y$_{12}$ Inhibitors:

<table>
<thead>
<tr>
<th></th>
<th>TRITON</th>
<th>PLATO</th>
<th>CHAMPION PH.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>Prasugrel vs. Clopidogrel</td>
<td>Ticagrelor vs. Clopidogrel</td>
<td>Cangrelor vs. Clopidogrel</td>
</tr>
<tr>
<td><strong>ACS</strong></td>
<td>100%</td>
<td>100%</td>
<td>44%</td>
</tr>
<tr>
<td><strong>IIb/IIIa Inhibitors</strong></td>
<td>54.5%</td>
<td>26.6%</td>
<td>none</td>
</tr>
<tr>
<td><strong>Duration of Medication</strong></td>
<td>6-12 months</td>
<td>median 9 months</td>
<td>48 hours</td>
</tr>
<tr>
<td><strong>Primary Efficacy Endpoint</strong></td>
<td>D/MI/Str</td>
<td>D/MI/Str</td>
<td>D/MI/IDR/ST</td>
</tr>
</tbody>
</table>

SCAI  SACIS 2016
### Pivotal Studies with these three P2Y$_{12}$ Inhibitors:

<table>
<thead>
<tr>
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<th>TRITON</th>
<th>PLATO</th>
<th>CHAMPION PH.</th>
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<tr>
<td>Prasugrel vs. Clopidogrel</td>
<td>Ticagrelor vs. Clopidogrel</td>
<td>Cangrelor vs. Clopidogrel</td>
<td></td>
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<td>D/MI/IDR/ST</td>
</tr>
</tbody>
</table>

An evidence-based recommendation is not possible.
2014 ESC/EACTS Guidelines on myocardial revascularization

**Antiplatelet Therapy for Primary PCI - STEMI**

**Recommendations for antithrombotic treatment in patients with STEMI undergoing primary PCI**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiplatelet therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 80–150 mg i.v.) and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>It is recommended to give P2Y₁₂ inhibitors at the time of first medical contact.</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

*In STEMI, Pretreatment is a Class I Recommendation!*

EHJ, 35: 2541-2619, 2014
# 2014 ESC/EACTS Guidelines on myocardial revascularization

## Antiplatelet Therapy for Primary PCI - STEMI

**Recommendations for antithrombotic treatment in patients with STEMI undergoing primary PCI**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Grade</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasugrel (60 mg loading dose, 10 mg daily dose) if no contraindication</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Ticagrelor (180 mg loading dose, 90 mg twice daily) if no contraindication</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

EHJ, 35: 2541-2619, 2014

SCAI

SACIS 2016
2014 ESC/EACTS Guidelines on myocardial revascularization

Antiplatelet Therapy for Primary PCI - STEMI

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<tbody>
<tr>
<td>• Prasugrel (60 mg loading dose, 10 mg daily dose) if no contraindication</td>
</tr>
<tr>
<td>• Ticagrelor (180 mg loading dose, 90 mg twice daily) if no contraindication</td>
</tr>
<tr>
<td>• Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated.</td>
</tr>
</tbody>
</table>

EHJ, 35: 2541-2619, 2014

SCAI

SACIS 2016
2014 ESC/EACTS Guidelines on myocardial revascularization

What about Cangrelor?
Altogether, cangrelor seems to be a good therapeutic option in P2Y$_{12}$ inhibitor-naïve patients undergoing coronary stent implantation. It should be pointed out that there was no effect on mortality and that the benefit of cangrelor was mainly derived from preventing intraprocedural stent thrombosis.\textsuperscript{853}

In addition, the use of cangrelor allows platelet inhibition to be maintained up to surgery in patients discontinuing oral antiplatelet therapy, without any excess of perioperative bleeding, in contrast to interruption of oral P2Y$_{12}$ several days before CABG surgery.\textsuperscript{854}

Cangrelor has not yet been approved by the European Medical Agency or the Federal Drug Administration and therefore no specific recommendation about its use can be given.
2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Cangrelor may be considered in P2Y$_{12}$ inhibitor–naive patients undergoing PCI.

European Heart Journal Advance Access published September 11, 2015
Cangrelor was considered appropriate for a NICE technology appraisal. NICE is unable to make a recommendation about the use in the NHS of cangrelor for reducing atherothrombotic events in people with coronary artery disease undergoing PCI (or in people awaiting surgery requiring interruption of antiplatelet therapy).

**Estimated impact for the NHS**

Based on the evidence and licensed indication, cangrelor is a second-line treatment option. It should be considered only when treatment with oral antiplatelet agents is not feasible or desirable. During assessment of the marketing authorisation application for cangrelor, the Committee for medicinal products for human use (CHMP) stated that the benefit of cangrelor was modest but noted that intravenous administration of an antiplatelet agent with a fast offset of action can be useful in selected people undergoing PCI.
WHAT WE DON’T KNOW

Different combinations of antiplatelets (eg, integral or crushed oral tablets and i.v. P2Y12 inhibitors or GPI) and anticoagulants (eg, heparins or bivalirudin) must be tested evaluating risk/benefit offsets and costs in order to determine the optimal pharmacologic approach to the patient undergoing PPCI.
Summary

• As compared to Clopidogrel, all three drugs are superior in reducing ischemic events including stent thrombosis.
• For STEMI, the ESC guidelines highly recommend the pretreatment with a P2Y$_{12}$ inhibitor as soon as possible / at first medical contact.
• Prasugrel / Ticagrelor should be preferred over Clopidogrel - if not contraindicated.
TAKE-HOME POINTS

• How much evidence before you adopt?

• PERSONALLY,
  • If not pre-loaded would consider cangrelor in STEMIls (especially with no aspirin on board – NO DATA for this)
  • If pre-loaded, might still consider cangrelor on a case-by-case basis
    • Experience reduced bioavailability as a consequence of nausea, use of opiates or impaired gastrointestinal absorption.
    • People in an unconscious state undergoing emergency PCI in whom bleeding risk is deemed to be low.
  • People with an unclear coronary anatomy and where early administration of a long acting P2Y12 inhibitor may increase clinical risk (for example, aortic dissection or rupture, Esophageal tear, pericarditis).

• Cost is a consideration
THANKS
Prehospital Ticagrelor in ST-Segment Elevation Myocardial Infarction

TIMI MAJOR BLEEDING (≤30 days)

- Prehospital: 1.3%
- In-hospital: 1.3%

P-value = 0.91
Stent Thrombosis in patients according to antithrombotic agent

<table>
<thead>
<tr>
<th>Antithrombotic</th>
<th>Cangrelor</th>
<th>Clopidogrel</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bivalirudin only</td>
<td>7/1014 (0.7%)</td>
<td>15/1045 (1.4%)</td>
<td>0.48 (0.19, 1.18)</td>
<td>0.456</td>
</tr>
<tr>
<td>Heparin only</td>
<td>36/3800 (0.9%)</td>
<td>51/3766 (1.4%)</td>
<td>0.70 (0.45, 1.07)</td>
<td></td>
</tr>
</tbody>
</table>

White HD, et al. JACC Interv. 2015;8:424–33

### Independent predictors of IPST

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR [95%CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI (vs. stable angina)</td>
<td>1.87 [1.04,3.36]</td>
<td>0.04</td>
</tr>
<tr>
<td>NSTE-ACS (vs. stable angina)</td>
<td>2.07 [1.26,3.40]</td>
<td>0.004</td>
</tr>
<tr>
<td>Thrombus at baseline</td>
<td>1.79 [1.12,2.84]</td>
<td>0.01</td>
</tr>
<tr>
<td>Total stent length (per 1 mm↑)</td>
<td>1.03 [1.02,1.03]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cangrelor (vs. clopidogrel)</td>
<td>0.65 [0.42,1.00]</td>
<td>0.048</td>
</tr>
</tbody>
</table>

* Other variables in the model: Current smoker, number of PCI vessels, DES vs. BMS, TIMI flow at baseline, US vs. non-US site

**IPST in CHAMPION PHOENIX**

10,939 pts assessed by a blinded core lab

**Impact of IPST on 48-hour and 30-day adverse events**

<table>
<thead>
<tr>
<th>48-hour endpoints</th>
<th>IPST</th>
<th>No IPST</th>
<th>Adjusted OR [95%CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/MI/IDR/ARC-ST</td>
<td>29.2%</td>
<td>4.5%</td>
<td>11.85 [7.08,19.84]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death</td>
<td>5.6%</td>
<td>0.3%</td>
<td><strong>20.82 [7.34,59.02]</strong></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ARC Definite ST</td>
<td>3.4%</td>
<td>0.3%</td>
<td>12.15 [3.46,42.68]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IDR</td>
<td>4.5%</td>
<td>0.6%</td>
<td>10.32 [3.50,30.37]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MI</td>
<td>25.8%</td>
<td>4.0%</td>
<td>12.00 [6.97,20.64]</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>30-day endpoints</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/MI/IDR/ARC-ST</td>
<td>31.5%</td>
<td>5.7%</td>
<td>9.65 [5.86,15.89]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death</td>
<td>10.1%</td>
<td>1.0%</td>
<td><strong>12.25 [5.76,26.05]</strong></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ARC ST</td>
<td>5.6%</td>
<td>0.8%</td>
<td>7.56 [2.91,19.65]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ARC Definite ST</td>
<td>4.5%</td>
<td>0.6%</td>
<td>8.17 [2.81,23.77]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IDR</td>
<td>5.6%</td>
<td>1.1%</td>
<td>6.36 [2.46,16.40]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MI</td>
<td>27.0%</td>
<td>4.4%</td>
<td>11.34 [6.66,19.30]</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Propensity score adjusted for: age, gender, smoker, region US vs. OUS, race, weight, biomarker, previous MI, (stable angina vs. NSTEMI, previous PCI, previous CABG, peripheral artery disease, patient presentation, worst pre-procedure TIMI score, stent type, bifurcation treatment, aspirin dose, number of treated vessels, clopidogrel loading received, clopidogrel loading dose (300 vs. 600 mg), canagrelor infusion duration, bivalirudin received.

IPST in CHAMPION PHOENIX

10,939 pts assessed by a blinded core lab

Impact on 30-day ARC stent thrombosis (out of lab)

IPST: 89 82 79 77 77 77 76
No IPST: 10850 10755 10722 10708 10699 10691 10653

No at risk:

<table>
<thead>
<tr>
<th>Days from Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>0  5  10  15  20  25  30</td>
</tr>
<tr>
<td>IPST  8  8  5  5  5  5  5</td>
</tr>
<tr>
<td>No IPST 305 305 305 305 305 305 305</td>
</tr>
</tbody>
</table>

HR [95%CI] = 7.66 [3.11, 18.85] 
P<0.0001

Pharmacodynamic Effects During the Transition Between Cangrelor and Ticagrelor

Conclusions Ticagrelor given before or during infusion of cangrelor did not attenuate the pharmacodynamic effects of cangrelor. The pharmacodynamic effects of ticagrelor were preserved when ticagrelor was given during infusion of cangrelor. Consistent with the reversible binding of ticagrelor, this oral P2Y₁₂ antagonist can be administered before, during, or after treatment with cangrelor. (J Am Coll Cardiol Intv 2014;7:435–42) © 2014 by the American College of Cardiology